Synthesis of α-Hydroxychalcones

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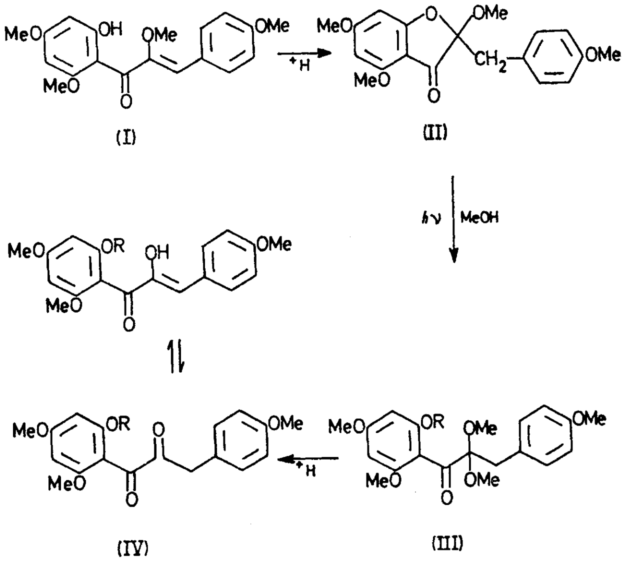
Summary α-Hydroxychalcones have been synthesised from α-methoxychalcones; this general method enables a study of the keto–enol tautomerism of 2′-methoxy-α-hydroxychalcones.

WATER solubility, achromatism, and their natural occurrence as *geometrical* isomers (enolic tautomers) are properties of a new class of α-hydroxychalcones which differ from those of their conventional counterparts.[1–4] Members of this new group have been characterized as 2′-hydroxy-α-methyl ethers, thus precluding confirmation of the natural presence as keto tautomers, as previously inferred from the above properties.[5]



Direct synthesis of substituted α-hydroxychalcones by routes similar to those used for α-methoxychalcones (*i.e.* Hoesch synthesis of 2,2′-dihydroxyacetophenones and their aldol condensation with aryl aldehydes) presents difficulties because of the problem of obtaining anhydrous hydroxyacetonitrile for the initial step. Earlier investigations on the conversion of the oxirane ring of chalcone epoxides for the synthesis of the parent 1,3-diphenylpropane-2,3-dione,[6] led in one instance to 2′-benzyloxy-6′-methoxy-α-hydroxychalcone *via* alkaline hydrolysis,[7] but the variable course of the reaction is dependent on the character of the substituents in the molecule and consequently this approach does not constitute a general synthesis. These difficulties (*cf.* also ref. 8) have now been circumvented through an indirect synthesis which promises to be of general applicability.

The chalcone (I),[9,10] m.p. 120—121°, was converted, under acid conditions, into (II) (maesopsin tetramethyl ether[10]), m.p. 131°. Photolysis of the latter at 300 nm in absolute methanol gave (III R = H) (52%) m.p. 114°, $\nu_{\max}^{\mathrm{CHCl_3}}$ 1627 cm^{-1}, τ ($CDCl_3$) −1·30 (s, 2-OH), 6·40 (s, CH_2), 6·70 (s, 2 × OMe). Methylation of the 2-hydroxy-group with diazomethane gave the fully methylated ketal (III; R = Me), m.p. 141°, $\nu_{\max}^{\mathrm{CHCl_3}}$ 1698 cm^{-1}. The latter (III; R = Me) is readily hydrolysed with 3N H_2SO_4 into (IV; R = Me) (42%), m.p. 136°, M^+ 344 (13·6%), *m/e* 195(100), 149(39), 148(99), $\nu_{\max}^{\mathrm{KBr}}$ 1680, 1720 (shoulder) cm^{-1} (high intensity broad band).

By contrast, hydrolysis of the 2-hydroxy-ketal (III; R = H) under weakly acidic conditions (0·1 N HOAc) to prevent cyclisation, gives a 1 : 2 proportion of a mixture of (I), m.p. 120°, and its *cis*-isomer, m.p. 116°, readily separable by t.l.c. in 1,2-dichloroethane–EtOAc (49 : 1). Similar hydrolysis of the acetyl derivative of the ketal (III; R = Ac) gave the 2-(4-methoxybenzyl)-2-hydroxybenzo[*b*]furan-3-[2*H*]-one analogue only.

A parallel sequence of conversions starting with naturally derived 2-(3,4-dimethoxybenzyl)-2,6,7-trimethoxybenzo-[*b*]furan-3[2*H*]-one[11] has been completed.

The α-hydroxychalcone (IV; R = Me) in solution ($CDCl_3$–C_6D_6) consists (n.m.r. spectra) of 40—45% keto-tautomer in equilibrium with a 1 : 1 mixture of *trans*- and *cis*-enolic forms in $CDCl_3$–C_6D_6, the proportions varying somewhat with the solvent ratio. I.r. spectra of crystals again indicate the presence of the α-diketo form ($\nu_{\max}^{\mathrm{KBr}}$ 1720 cm^{-1}). The apparent ease of interconversion of tautomers (*cf.* also ref. 6) and the high proportion of the keto-form rationalizes the observed high mobility of free phenolic forms on cellulose substrates in aqueous medium, and reflects on their suggested[3,5] ease of translocation in plants.

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